



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

93180d

Food and Drug Administration  
Center for Biologics Evaluation and Research  
1401 Rockville Pike  
Rockville MD 20852 1448

April 15, 2002

By Certified Mail – Return Receipt Requested  
and by Facsimile Transmission

CBER – 02 – 011

Warning Letter

Louis R. Bucalo, M.D., Chairman  
Titan Pharmaceuticals, Inc  
400 Oyster Point Blvd., Suite 500  
South San Francisco, California 94080

Dear Dr. Bucalo

During the inspection that ended on September 19, 2001, Rochelle B. Young, an investigator with the Food and Drug Administration (FDA), reviewed the activities of your firm, Titan Pharmaceuticals, Inc. (TPI), as a sponsor and a contract research organization shipping investigational products used in clinical studies. The inspection was conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational drugs.

At the close of the inspection, a Form FDA 483, Inspectional Observations, was issued to Sunil Bhonsle, Executive Vice President, TPI. We reviewed the letter dated October 1, 2001, sent by your firm in response to the Form FDA 483.

We have determined that your firm violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Part 312 (available at <http://www.access.gpo.gov/nara/cfr/index.html>). The applicable provisions of the CFR are cited for each violation listed below.

1. **Your firm failed to ship investigational new drugs only to investigators participating in the investigation. [21 CFR § 312.53(b)].**

In May 2001, your firm shipped the wrong investigational vaccine to a clinical investigator who was not conducting a study for that test article. While the vial labels identified the test article that was shipped, it was not the test article that was intended for use with the type of cancer in the investigator's protocol.

A factor contributing to this serious shipping error was your firm's lack of written Standard Operating Procedures (SOPs) for the distribution of test articles. According to the TPI letter dated 10/1/01, your firm has prepared and put into effect written SOPs for this purpose.

**2. Your firm failed to maintain adequate records showing the shipment of investigational drugs. [21 CFR § 312.57(a)].**

- A On five occasions between March and June 2001, the packing slips accompanying shipments of TPI products erroneously identified the test articles as the ones requested by the staff for use at clinical sites and not the actual products that were shipped.
- B On nine occasions, between February and August 2001, your firm shipped boxes containing packing lists that failed to correctly identify the enclosed test articles. The packing lists were incorrect, but the packages contained the correct test articles.
- C Your firm sent six letters to clinical sites identifying two lots of an investigational vaccine as a similar, but separate and distinct, product. The letters referred to the test articles in lot numbers and as " ". However, during the inspection, your staff provided documentation that the test articles in both of these lots are " ". The failure of your staff to properly identify two similar investigational products in an accurate and consistent manner is indicative of systemic training and record keeping problems.
- D For 16 of 68 shipping records reviewed, the TPI authorization to ship the investigational product was not signed and dated. According to the TPI letter dated 10/1/01, authorization for shipment of investigational products by your firm will be signed and dated, as well as subjected to a second review and approval that is also signed and dated.

This letter is not intended to be an all-inclusive list of deficiencies. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations.

Please notify this office in writing, within fifteen (15) business days after receipt of this letter, of the specific actions you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Failure to promptly correct these deviations may result in enforcement action without further notice. These actions could include termination of Investigational New Drug Applications and/or injunction.

Please send your written response to:

Mary Andrich, M.D.  
Division of Inspections and Surveillance (HFM-664)  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
1401 Rockville Pike, Suite 200N  
Rockville, Maryland, 20852-1448  
Telephone: (301) 827-6221

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,



Steven A. Masiello  
Director  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research

cc:  
Dennis K. Linsley, Director  
Food and Drug Administration  
1431 Harbor Bay Parkway  
Alameda, California 94502-7070